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Ethical aspects of vaccines and vaccination

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Traditional certainties no longer serve our societies as well as they might. Technical developments over a broad range of engineering disciplines have radically changed the nature of the physical world in which we live. Our knowledge base has expanded concurrently, enabling us to provide materially based and more convincing answers to questions which baffled our antecedents of 200 years ago. This requires that we review and reconsider the ethical guidelines for behaviour which have been largely founded on philosophies and concepts whose origins may be traced back to between 1000 and 3500 years ago. An example of the implications of these changes may be seen in the area of vaccines and vaccination which evinces the pressing need to review traditional ethical positions to take the maximum advantage of the potential for animal and human benefit inherent in this prophylactic approach to healthcare.

In this paper I examine some of the general ethical issues thrown up by recent advances in the field of vaccines and vaccination. It will touch on issues of the putative autonomy of the individual and way we will have to reassess the cost ((risk * the magnitude of the damage) + cost of manufacture and distribution + surplus) to benefit relationship. Issues subtended from the effect of vaccines on the magnitude of populations will be followed by transcultural issues implicit in vaccine testing and delivery. The use of vaccines to obviate behavioural changes (technical fixes), generate transcendental concerns and provide new threats via biological warfare agents will also be treated.

THE AUTONOMY ISSUE

It is part of current medical practice when dealing with patients to extol four basic ethical principles: autonomy, beneficence, non-maleficence and justice. However, when we consider issues related to vaccination the principle of autonomy (self-determination; freedom from interference unless the act harms others (J.S. Mill); as in UN or CfE declarations on human rights) is challenged. While the principle of autonomy may be asailed from a number of different facets such as the competence of an individual to provide informed consent, the rights of a fetus if the pregnant mother decides to be immunized or the implicit implications of the social contract entered into when an individual choses to dwell in a particular society, I will examine in more detail a further issue involving the expression of social responsibility.

It is well known that when a high proportion of a population is vaccinated, those who have not been immunized become protected by the decrease in the level of the pathogenic organism (the herd effect). The question which this poses is, do those who have opted against vaccination have the right to benefit from the expense and the risks of vaccine-induced damage accepted by those who have been vaccinated? Not only that, but such unvaccinated individuals pose a threat to the vaccinees as they serve as a reservoir in which the disease can be maintained and propagated. Were the society to collectively determine that all its citizens should receive the vaccine then the principle of patient autonomy is infringed. An intermediate position might be to levy a special cash buy-out dispensation to those who refuse vaccination as a contribution to the costs incurred by those who have accepted the risks of vaccine-induced damage. Whatever the outcome in any particular society it is clear that vaccination poses a challenge to accepted ethical positions, the resolution of which will be dependent of the degree of social coherence and farsightedness.

COST/BENEFIT CONSIDERATIONS

For much of the last 350 years commercial companies have been required to provide products to the marketplace and society's judgement on the company has been via the acceptability of the product at the price demanded. The function of the company was to accumulate profits for its shareholders and top managers (incentives) and society did not interfere with the way the product was made, nor with the product spectrum on offer. This ethic too, is in need of review. Vaccines are a clear benefit to society as a whole. However, there is a risk of vaccine-induced long-term and severely debilitating damage [well recognized for Polio vaccines and less well established for any other vaccine cf. Swine Fever (inactivated influenza) Vaccines and Guillain-Barré syndrome] which is especially poignant when incurred after the vaccination of a 3-month-old healthy infant. Under present conditions the manufacturing company may be sued for damages both actual and punitive (if wilful negligence is proven). But is this the appropriate ethic? May not the society, in accepting the benefit of widespread vaccination, compensate those who suffer damage at a level communsurate with the damage? Of course, were the manufacturer culpably negligent in a procedural

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matter, then compensation would also be due from that source.

Resulting from this liability situation, vaccine manufacturers are reluctant to venture into vaccine projects. Also, as the cost of obtaining a product license is estimated to be some $200–600 million, the implications for the cost of a dose of vaccine is more driven by the cost of the regulatory procedure than the production cost (which rarely exceeds the cost of the bottle plus label). The ethical issue here is whether the regulatory hurdle which has to be overcome is really operating in society's best interests. Nothing we eat or do is without the risk of incurring damage. Vaccines are not different in that respect. Yet the cost of obtaining a license to manufacture and distribute implies that the cost of the vaccine has to be many dollars merely to recoup the costs involved. Does this mean that the rich should pay a high price for a vaccine and thus subsidize the provision of cheap vaccines to the poor? Or is it the job of the elected representatives of the people to act as purchaser on behalf of the poor and provide the vaccine manufacturer compensation through the tax system or other fiscal dispensation?

Vaccines for diseases which afflict a few are not a commercial proposition unless communal support is provided. Vaccines which lead to a decrease in the need for over-the-counter or prescribed medicaments are also unlikely to be made by commercial concerns. The reluctance of pharmaceutical companies to work-up a vaccine for *Helicobacter pylori* which would prevent the recurrence of stomach ulcers and hence stomach cancers is evident from the research programmes of those companies which make anti-ulcer drugs. Research on vaccines which would prevent the common cold (caused by a combination of *Rhinoviruses, Coronaviruses* and *Adenoviruses*) is also conspicuous by its absense. But prophylaxis as an approach to healthcare is also underfunded by society at large. Therapeutic research receives over 10 times the funding of prophylaxis; and this is particularly difficult to understand when there are many inexpensive ways of achieving prophylaxis, of which vaccination, which affects the immune system, is but one. Other methods of prevention focus on the protection of the immune system to decrease the probability that it will be overwhelmed by an endogenous or exogenous pathogen; such procedures may be termed 'Fence Vaccines'[1].

A new relationship between industry and the community is indicated. The former is now required to recognize that it will be judged as much by the ethicality of its actions as the efficacy of its products. For the pharmaceutical industry, ethics is not an optional extra; it is essential.

POPULATION CONSIDERATIONS

An ethical argument which is proscriptive of the use of vaccines in the developing and less developed world (containing 79% of the world's 6.1 billion people) is that they will lead to an increase in an already unsustainable population. This will have sequellae via an increase in suffering from malnourishment, population migrations and war. However, recent figures published by UNICEF refute these projections[2] and show that the average number of children born to a woman of the developing world throughout the period of her fertility has dropped from 6.06 to 3.75 between 1960 and 1994. This would indicate that more, rather than fewer, vaccines are required; and indeed vaccines protective to the diarrhoeal and respiratory diseases of childhood are on test in the field, while candidate vaccines aimed at controlling malaria languish in laboratory fridges.

Population may not only be affected by a decrease of infant mortality but also by an increase in the average age of the community. As the level of communicable disease wanes, people live longer and society then has to adjust its working conditions such that there are productive positions for the older people to occupy. It is clearly not practicable to socially provide for protracted retirements, so the emphasis on life-long learning, skill changing, job flexibility and part-time working will become the norms of future social development.

TECHNICAL FIXES

Is it appropriate to use a technical fix when an almost cost-free change of behaviour will achieve the same effect? Such an ethical problem is thrown up by the willingness of our communities to spend billions of dollars to provide therapeutic and prophylactic agents to control the spread and effects of the Human Immunodeficiency Virus (HIV), while the disease would be eliminated were people to engage in safe, condom-protected, intercourse in their pre- or extra-marital sexual relationships where the prospective partners had not been thoroughly tested for the presence of serum antibodies to the virus. This provision also applies to the transmission of the viruses which cause Hepatitis B, genital herpes, as well as the cancers wrought by the Papilloma virus. As a corollary to the practise of safe sex, it might also be expected that gonorrhoeal infections would decline, as would those caused by *Treponema syphilis* and the yeast *Candida*.

Many of the food- and water-borne diseases caused by bacteria of the *Salmonella, Escherichia, Shigella, Listeria, Campylobacter* and *Vibrio* groups would be eliminated were drinking and washing water to be prepared according to the highest standards prevalent in most Developed Countries. However, the engineering requirements to achieve this in the short term are daunting, whereas the prospect of the development of orally deliverable vaccines which would provide protection against the diseases caused by the above pathogenic bacteria is a task which may be brought to a successful conclusion within the next decade.

A further case where vaccines are used to preclude the expenditure of monies is to protect people from the effects of the diseases of propinquity; typhus and tuberculosis. Both of these diseases flourish when people are housed in crowded insanitary conditions. It may be that the vaccination route is cost-effective in monetary terms but this should not be used as a way of avoiding the social improvements which would enhance

the dignity of citizens, as well as improving their health.

TRANSCULTURAL ISSUES

Infectious disease-causing organisms do not recognize national boundaries. Transworld travel for tourism and business is increasing exponentially and with it are opportunities for disease-causing organisms to travel. We are also presented with a situation in which tests of vaccines in Developing Countries can be effected at considerably less expense than in a Developed Country. This has led to a series of ethical issues which are exacerbated by the different cultures of the people who may be engaged in the vaccine trials. For example, is it possible to obtain the informed consent of a person who is illiterate and who does not understand the implications of something like a vaccine with which (s)he is totally unfamiliar? A second issue might be that the removal of blood or tissue for sampling might be regarded as an attempt to capture the spirit of the so deprived individual. Additionally, there may be taboos about removal of blood via venipuncture and in some cultures the insertion of needles into bodies may have overtones not foreseen in Western cultures.

On removal of a sample containing cellular material from the body of an individual (generally a tissue responsible for a pathogenic effect) one obtains the opportunity to work with a highly selected and unique genome. Were the genes of that cell to be used to make a pharmaceutical to particularly benefit people in the Developed World, what sort of compensation should acrue to the source of the cell line from which the gene was obtained? Current thinking by the Nuffield Ethics Committee[3] would have it that the cell provider has not contributed to the inventive step in the drug or prophylactic development and therefore is not to be compensated. However, if advantage is taken of the uniqueness of the material derived from a person of the Developing World then it would be churlish not to recognize this through some financial contribution to the individual and his/her community.

One might ask, to what extent is a prophylactic trial in the Developing World relevant to the circumstances prevalent in the Developed World? Are the conditions leading to infection and the challenge organisms relevant? Are the people in whom the vaccine is tested likely to respond in an immunologically equivalent manner when the history of the exposure of their immune systems to disease is dissimilar in many ways to a person of the Developed World? In the event that there is damage to an individual as a result of exposure to vaccine in a trial, what are the levels of compensation and who pays? And indeed, is it ethical that a person in the vaccine-producing country should enjoy the benefits which have been won at the expense of the risk-taking of a person in less privileged circumstances? To some extent many of these questions may have answers were the Developed Country vaccine producer to agree up-front to provide cost-free vaccine to all the people of the country in which the vaccine trial had been effected. In that way something of a bargain may be established such that overt exploitation has been subverted into mutual gain.

In all such situations it would not be an acceptable ethic to effect trials with placebo controls which did not provide the best possible protection. Similarly it would be counterproductive to use vaccines whose safety was an issue and where a less damaging vaccine could be made available, albeit at greater expense. In addition, there is the overriding consideration that if nothing is attempted then there would be a known tally of deaths and disease and our efforts to combat that embody a justification for effecting vaccine experimentation.

INVOLVING THE TRANSCENDENTAL

A definition of the transcendental might be 'that which is outside the cause-and-effect system', where the latter implies that all which exists and the way it interacts is delimited by the energy and matter of its constitution. For example, ghosts, fairies, trolls, spirits, jinn and souls are described in such a way that they perform their tasks with scant regard for the properties of matter and energy, as do the panoply of deities which have been posited as having creative and control capabilities with regard to the affairs of humans. Nevertheless, such considerations cannot be obviated when we review the reactions of community members to the production and use of vaccines, particularly when some of the most emphatic proscriptive reactions emanate from the leadership of recognized deitic religions.

In Kirkpatrick's book on inoculation published in 1761[4] there is the astonishing report of the abreaction of the church to vaccination because, as a result of the possibility of dying from the vaccine of the day (smallpox, occasionally contaminated with syphilis), it may be construed that the vaccinee was indeed seeking to commit suicide, which was sinful. In modern times there were a series of reports in the UK media[5] wherein the Catholic church was seeking to prevail on its susceptible female members to forego vaccination protective against Rubella, as the vaccine was prepared from the cells of an aborted human fetus: for human abortion is contrary to the teachings of that church.

On a more esoteric plane, it is possible to argue that, through the use of vaccines, mankind has developed a capability which may eventually rid the world of those infectious microoganisms which have been the bane of our struggle to survive. This depletion of the deitic armamentarium may be construed as seeking to deny the deity of one of its controlling effector systems; namely, the threat of divine retribution through the causation of plagues[6]. Alternatively, it may be held with equal rectitude, that the deity ordained us to discover and use vaccines as part of its (undisclosed) master plan. Consonant with this latter controversy, there are those who assert that it is unnatural to disturb the ways of nature and as vaccines are a creation of mankind, they are not natural and are therefore to be condemned. As this contention rests on the definition of what is natural it is possible to reconstrue this issue totally were we to assert that whatever exists is natural; merely by virtue of its existence. It would follow that there does not exist anything which is artificial (in the sense of unnatural) which implies that all the products of the arts (techniques, crafts, skills) of

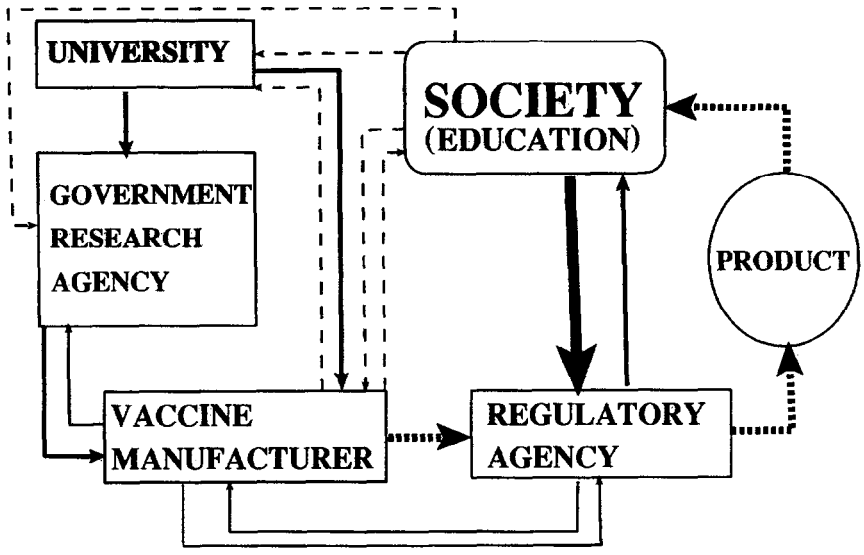

Figure 1 The Inner Circle of Associated Agencies leading to the production and use of a vaccine

humans (and animals) are natural and are incorrectly designated as artificial unless the meaning of that term were changed to its more appropriate designation, as works which are the product of humankind's arts (hence arti-ficial; made by art).

Now that it is practicable to identify a defective gene in an adult, child or even embryo, techniques are in development to repair, exchange or inactivate that gene specifically. These methods imply the existence of 'genetic vaccines'. However, these self-same methods may be used not just to correct defects but to enhance characteristics we may desire to accentuate[7]. As the word 'disease' is defined as a state of being in which one is not-at-ease, it is not difficult to use the word to describe a situation where a person is not at ease with their height, intelligence, running or ageing, speed etc. This raises the ethical question of the use of genetic vaccines to prevent the disease resulting from such deeply held feelings. There is little doubt that the remediation and/or prevention of situations which cause physical pain is encouraged and applauded by society. The same cannot be asserted where the pain

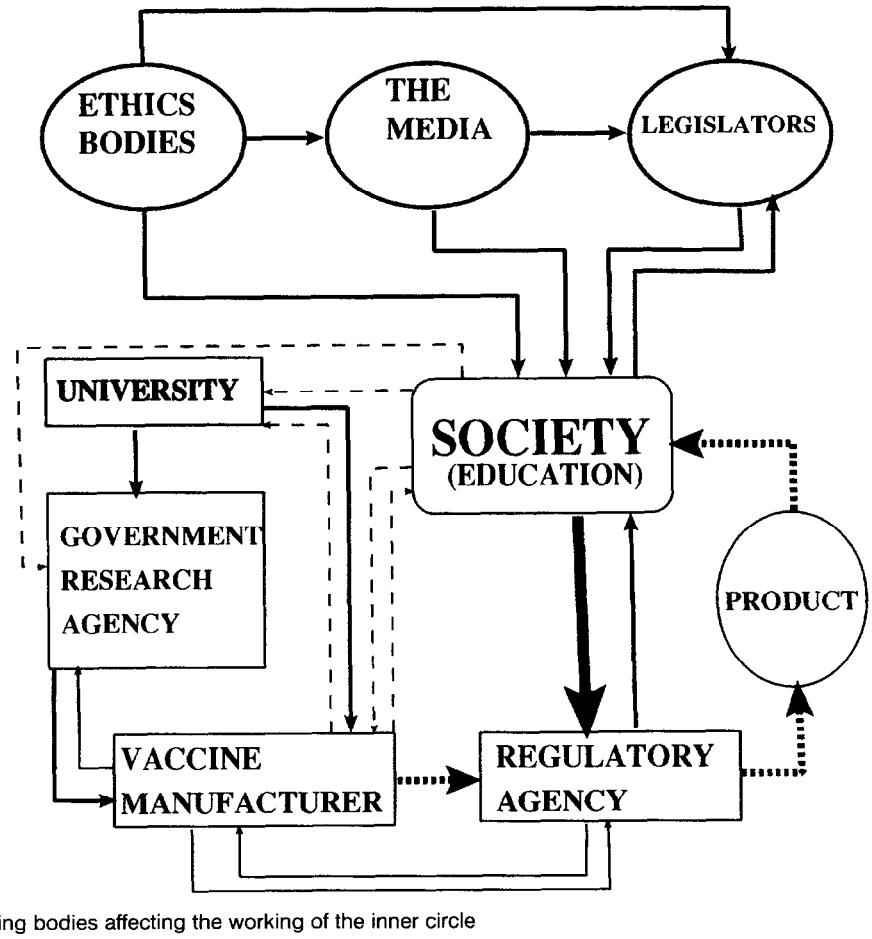

Figure 2 The Controlling bodies affecting the working of the inner circle

may be psychological. Nevertheless, this latter pain is just as actionable as the physical pain (indeed it is physical, but of the activities of the brain as opposed to muscle). Indeed, not only would we relieve suffering but we might also achieve a human being who is more functionally capable of making a more extensive contribution to society; a feature which is not given to all pain-killing remedies. That such measures might be construed as interfering with some transcendental plan cannot be denied, but the ethic of beneficence might be applied to progress the use of these genetic vaccines in all their manifestations.

Were we to have an effective orally deliverable contraceptive vaccine[8] (pregnancy results from the infection of the female by a male spermatozoan) then ethical considerations will be required to determine the way in which such a powerful tool for population control might be used. The contamination of drinking water supplies with a contraceptive vaccine would act counter to the autonomy principle of ethics and could be held to be an affront to the dignity of humanity in denying individuals control over their own fertility. Notwithstanding this clear ruling, it is possible to conceive of conditions in which a decrease in population levels is an urgent necessity and the use of an orally delivered contraceptive vaccine might be the only way of achieving that end without recourse to widespread sterilization. As with any other tool, we have to adopt an ethic which permits its appropriate use; what we need to do ahead of time is to discuss and debate what those circumstances might be.

VACCINES AND BIOLOGICAL WARFARE

Anthrax bacteria, botulinum toxin, the plague bacillus (*Yersinia pestis*), measles and influenza viruses have all been proposed as agents of human destruction in the context of international and intranational conflict. Both smallpox and measles have been implicated in the decimation of the indigenous populations of the Americas during the colonization processes beginning in the 1600s. Vaccines protective against these diseases, therefore, become defensive devices which would have to be surmounted by a would-be aggressor. Genetic engineering may be used to attempt to enhance the lethality of existing agents or make otherwise benign

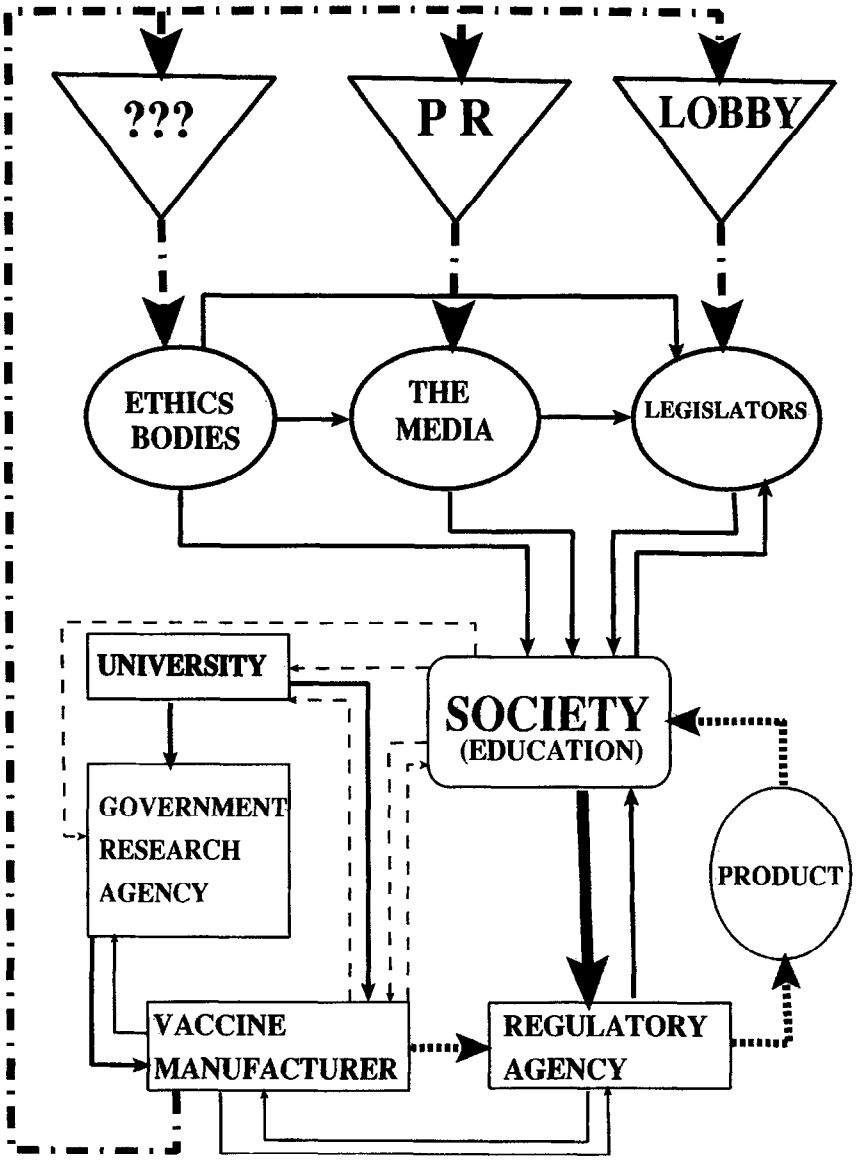

Figure 3 Adding an ethical dimension to industry's external relationships

agents lethal. It is unlikely that an increase in lethality can be achieved through the manipulation of the genes which code for toxin structure, for the sophistication of the binding site of these toxins, coupled with the evolution of the enzyme which causes the damage, has probably reached the maximum level of efficacy as a result of the evolutionary process by which it was formed. The addition of new strain of toxin genes to a particular bacterial cell may also be assayed. But the common pattern of bacterial toxins leads to vaccine solutions which are likely to be cross-protective, irrespective of how many toxin genes are compiled in any one bacterial cell.

Perhaps, of more serious consequence, would be the engineering-out of the epitopes which evoke the immune system to produce toxin-neutralizing antibodies. When this occurs epitopes which heretofore were immunosuppressed become immunodominant[9]. This would call for the development of a new vaccine which could be made by using the newly engineered binding portion of the toxin molecule to induce neutralizing antibodies to the fully constituted toxin (binding portion plus enzymatic component). This process could be repeated many times.

In addition to the manipulation of the toxin system, developments occur in the methods for the dissemination of the agents. While it is possible to conjure scenarios of contaminated water supplies and recognize that the air handling systems of large buildings may constitute a means of agent distribution, the mechanisms for the protection of such seemingly open targets are well in place already; for we do treat water supplies with inactivants and it is recognized that the circulation of air within air-conditioned buildings is fraught with problems if people's natural illnesses are circulated by air-handling equipment devoid of high performance filtration systems. To meet the contingencies of noxious agent distribution the stratagem of 'Fence Vaccination'[1] may be brought into play.

The cycle of measure/countermeasure with which we are familiar in the area of conventional and nuclear weapons has its echoes in the area of biological warfare. That we have a duty to defend the life of our peoples is an ethical principle which few would dispute. In the context of this paper, the pursuit of vaccines to existing and potential biological warfare agents is not just a job done in response to real or perceived threats but should become a mission whose importance ranks so highly that it has to be included with the strategic planning we have to undertake to survive. As in other areas of defensive reaction, we might expect the vaccine production techniques to be enhanced with regard to both the ability to manufacture high quality immunogenic preparations rapidly and also with respect to the engineering of those immunogens. These abilities will have spin-off effects with regard to our ability to produce vaccines protective against the biological agents which pose threats from natural sources, such as influenza viruses whose type changes require us to make immunogenically unique vaccines on a year-by-year basis. We have also to take note of the emergent infectious agents (Ebola, Hantavirus, HIV) which have achieved a degree of notoriety in recent years[10]. Our ability to respond to such agents has been slow, cumbersome, disorganized and paltry in relation to the importance of the test situation which these agents proffer. Our ethics require that we improve on this performance.

TOWARDS A NEW MISSION FOR INDUSTRY

Vaccine manufacturers must obtain a licence to enable them to market their vaccine products to the wider society. This licence is obtained on the recommendation of a body called a regulatory agency (the FDA division of Biologics in the USA, the Committee for Medicines in the UK, etc.). Obtaining regulatory agency acceptability[11] of a vaccine product is a process which may take 5–25 years and cost $200–600 million dollars. As can be seen from *Figure 1*, the regulatory agency is subject to being influenced by the society which it is set up to serve.

In addition to this necessary connection to the regulatory agency, industry may opt to receive from universities and publicly funded research institutes information and materials which enable it to embark on new vaccine projects.

This interaction between the private and public sectors is fraught with ethical problems stemming from the difference in the culture of the two types of institution[12]. This has been rendered particularly acute in recent years when attempts have been instigated to make the publicly funded institutions behave as if they were private, profit-making bodies. The insinuation of industrialists into the peer review process for grant applications generated by academics has been one area where the bicameral functionality of the seconded industrialist leads to the funding of conservative research projects which do not compete with the industrialist's undisclosed mission. In this, society is not well served by the monies it sets aside for both academic and publicly funded research.

Society is not amorphous. It has structure through its institutions. The institutions which affect the way the regulatory process works may be identified as being (1) the ethical bodies; (2) the media; (3) legislatures; and (4) the educational system (*Figure 2*). The ethical bodies include recognized religions whose leaders provide ethical guidance to the members which impinges on the production and use of vaccines, while bearing in mind current social exigencies. There are secular sources of ethical guidelines which are not as well organized and overt. Such individuals might recognize that ethics are not guidelines which are provided by the pronouncemnts of a deity but are rather the set points in the control system which modulates human social behaviour with the objective of promoting both the survival of the individual, society and other biotic entities as wealth and the occasion permits[13]. The media are informed by the religous ethicists as well as picking up on the raw nerve endings of the fears and sensitivities of their fellow socialites. They do not hesitate to evoke the image of the entity created by Victor Frankenstein at the prospects of the slightest opportunity of affecting a deliberate change to the genetics of the human species. Our tradition encourages us to regard monsters as the avenging agents of personal wrongdoing; so such buttons do not require much pressing to evoke negative reactions to

the prospects of experiments gone awry. The third effector on the way the regulatory agencies behave is the legislature. It is by law that pharmaceutical products have to be safe, efficacious and be made by a demonstrably consistent process. But how safe is safe? and what is efficacious? and what are the limits by which we define consistency? The answers to each of these questions pose ethical problems. It is recognized that a balance has to be struck between the urgency of the need (if we don't have the agent, people will die) and the side-effects of the product. Education is a key feature when we consider how humans behave socially. Some attribute the education of children to parents only, and see the education institutions as providing knowledge and capability, but not ethics. Others would have us believe that we receive effective training in ethics thoughout our lives from all kinds of sources of which educational institutions are prominent. It is a matter of choice as to whether an individual believes that 'you can't teach an old dog new tricks'. It is a matter of record that modern adults have to relearn their new car's control systems and idiosyncrasies each time they change their car. Learning to programme a video, access and use the internet, come to terms with computers, air travel and internationally derived food menues has come to many people late in life, yet they have made changes to their behaviours in the light of these new developments. We are indeed open to life-long education for which our modern universities are reorganizing.

These considerations provide opportunities for industry to accept a new mission. While they have accepted for many years the need for sympathetic public relations (with the media) and for lobbying activities (to affect the laws which receive legislative approval), they have not until now perceived that they have also to meet the challenge of ethics providers. This can be effected at two levels; the one, via the bodies which focus on the generation of ethical guidelines; the other, the educational system from the earliest grades to those who return to education in their third age or later. Industrialists will have to recognize that ethics matters. They will have to support institutions which engage in devising an ethics which is wholly compatible with living in a modern world with ever changing technologies and concepts about the nature of life and the way the world works. And they must engage in the promotion of ethics in a society which is hungry for a new ethical synthesis (*Figure 3*). All this has to be done at arm's length. There is no substitute for the realization that we all are members of the community and responsible in some measure for our mutual well-being: sectors cannot profit at the expense of other segments. This concurrence of aims needs a reaffirmation; it is hoped that industry will see its future success through the inclusion of this mission in its project portfolio.

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